

CALIFORNIA DEPARTMENT OF FOOD AND AGRICULTURE
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

FENOXYCARB

Ethyl (2-[4-phenoxyphenoxy]ethyl) carbamate

Chemical Code # 2283, Tolerance # 51317
SB 950 # Not assigned

5/19/88

Revised 9/8/89, 11/19/ 97, 11/21/97

I. DATA GAP STATUS

Combined, rat:	No data gap; no adverse effect
Chronic toxicity, rat:	No data gap; no adverse effect (see Combined, rat)
Chronic toxicity, dog:	No data gap; no adverse effect
Oncogenicity, rat:	No data gap; no adverse effect (see Combined, rat)
Oncogenicity, mouse:	Data gap; inadequate study; possible adverse effect indicated
Reproduction, rat:	No data gap; no adverse effect
Teratology, rat:	Data gap; inadequate study; no adverse effect indicated
Teratology, rabbit:	Data gap; inadequate study; no adverse effect indicated
Gene mutation:	No data gap; no adverse effect
Chromosome effects:	Data gap; inadequate studies; no adverse effect indicated
DNA damage:	No data gap; no adverse effect
Neurotoxicity:	Not required at this time

Toxicology one-liners are attached.

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

File name: T971119

Revised by Richard A. Duncan, 9/8/89; J. Gee, 11/19/97.

Rectified with Library records through volume 065, Record No. 132712.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED (CHRONIC/ONCOGENICITY), RAT

** 006 064954 "Fenoxycarb (Ro 13-5223/000): 104 Week Oral (Dietary Administration) Carcinogenicity and Toxicity Study in the Rat With a 52 Week Interim Kill," (Hazleton Laboratories, Europe Ltd, Lab Report No. 5191-161/123, 11/86). Ro 13-5223/000 Technical (purity = 96.6%) was fed in the diet to Crl:CD(SD)BR rats at 0, 200, 600 and 1800 ppm (60 rats/sex/group) for 104 weeks. An interim kill was made at week 52 (10/sex/group). NOEL = 200 ppm (increase in GOT, GPT and alkaline phosphatase levels; increase in mean relative liver weight; centrilobular hypertrophy of the liver--primarily in males--associated with focal necrosis and foci of pigmented histiocytes; focal fibrosis). No oncogenic effects were observed. **No adverse effect. Acceptable.** M. Silva, 5/19/88.

028 73123 Duplicate of 064954.

CHRONIC TOXICITY, RAT

See Combined, Rat.

CHRONIC TOXICITY, DOG

** 51317-024; 72978, 73119; "Chronic Toxicity Study Following Oral Administration of Ro 13-5223/000 (fenoxycarb), an Insect Growth Regulator, to Dogs for a Period of One Year"; F. Hoffman-La Roche & Co. Ltd., Basle, Switzerland, Research Report B - 153778; 6/30/88; Fenoxycarb, batch 2, purity = 96.6%; Dose levels 0 (empty capsules), 25, 80 and 260 mg/kg/day, in gelatin capsules, 7 days/week, 52 weeks; 4/sex/dose; No treatment-related effects were observed at 25 mg/kg/day were observed, at 80 mg/kg/day the only effects were the decrease in the mean absolute adrenal gland weight ($p < 0.05$, 80% of the control value) among males and a significant decrease ($p < 0.05$, 68% of the control value) in plasma inorganic phosphate was observed among males in week 52, at 260 mg/kg/day treatment-related effects included the decrease in the mean absolute adrenal gland weight ($p < 0.05$, 66% of the control value) among males, increases in relative liver (124% for males, 157% for females as compared to controls), testes (males only, 149% compared to controls) and kidney (females only, 121% compared to controls) weights, a decrease ($p < 0.05$, 54% of the control value for males and 50% of the control value for females) in plasma inorganic phosphate was observed among males and females in week 52; Dose response relationships are apparent for the decreases in the mean absolute adrenal weight among male dogs and the plasma inorganic phosphate observed in week 52 for 80 and 260 mg/kg/day; No treatment-related histopathology was observed at any dose level; **No adverse effects indicated; NOEL = 25 mg/kg/day; NOAEL \geq 260 mg/kg/day; Acceptable.** (Morgan, 6/8/89)

008 52977 Twenty-six week dog study. Not reviewed as of 11/19/97. (Gee, 11/19/97)

ONCOGENICITY, RAT

See Combined, Rat.

ONCOGENICITY, MOUSE

007, 025 064955, 073120 "Ro 13-5223/000: 80 Week Carcinogenicity/ Toxicity Study in Mice" (Inveresk Research International, Project # 430624, 3/87) Fenoxycarb technical, Ro-5223/000, Lot #2, 96.6% pure, was

administered in feed of CD-1 mice (50/sex/treatment for oncogenicity study) at 0, 30, 110, and 420 ppm (M) or 0, 20, 80, or 320 ppm (F); NOEL = 80 ppm (enlarged livers in high dose groups of both sexes). **Possible adverse effect:** an increase in lung alveolar/bronchiolar adenomas + carcinomas in 420 ppm males. Initially reviewed as unacceptable, upgradeable (dose justification, statement of purity of a.i. needed); rereviewed after submission of additional data; **unacceptable** (maximum tolerated dose not achieved). (Klein and Aldous 5/18/89)

065 132712 "Report of a potential adverse effect for fenoxycarb." (Ciba, 9/26/94) One page submission of incidences of pulmonary adenomas, pulmonary carcinomas and hepatocellular carcinomas in an ongoing study. Mice, 50/sex/group, were fed fenoxycarb in the diet for 18 months at 0, 10, 50, 500 or 2000 ppm. Preliminary incidence data showed a statistically significant increase in pulmonary adenomas in females (11/50 in high dose versus 1/50 in controls); in pulmonary carcinomas in males at 500 and 2000 ppm (10/50 and 10/50 versus 1/50 in controls) and in females at 2000 ppm (9/50 versus 2/50); and in hepatocellular carcinomas in males at 500 and 2000 ppm (18/50 and 22/50 with increasing dose versus 8/50 in controls). No worksheet. (Gee, 11/18/97)

REPRODUCTION, RAT

** 010 064959 "Ro 13-5223/000: 2 Generation oral (dietary administration) reproduction study in the rat". Hazleton Laboratories Europe, Ltd., Lab Report No. 4623-161/124, September, 1986. Fenoxycarb Technical, 96.6% purity, administered in feed at 0, 200, 600, and 1800 ppm. Parental NOEL = 200 ppm (relative liver weights increased in F at 600 ppm and in both sexes at 1800 ppm, with focal necrosis in M and hypertrophy in M and F adults at 1800 ppm; About 10% body weight decrements in F0 females and F1 M and F adults during growth phase). Reproductive effects LEL = 200 ppm [NO NOEL IDENTIFIED] (definitive weight gain decrements in 1800 ppm lactating rats, and apparent treatment-related weight gain decrements in 200 and 600 ppm lactating rats). The 200 ppm level is considered a **No Observable Adverse Effect Level** (NOAEL): No other reproductive parameters were affected by treatment, nor were there functional deficits in treated offspring at weaning, at any dosage level. **Acceptable**. C. Aldous, 4/22/88.

TERATOLOGY, RAT

009 064957 "Embryotoxicity Study in Rats With Oral Administration of Ro 13-5223/000. Segment II-Teratological Study With Post-natal Evaluations", (F. Hoffmann-La Roche, Inc., Ltd., Department of Reproductive Toxicology, Basle, Switzerland, Lab Report No. B-104875, 5/12/83). Fenoxycarb technical (purity \geq 93%) was administered to mated Fu-Albino rats (36/group) at 0 (vehicle = 4% carboxymethylcellulose, 0.9% NaCl, 0.5% benzyl alcohol, 0.4% Tween 80 in distilled water), 50, 150, and 500 mg/kg/day daily by gavage from days 7 to 16 of gestation (presence of a vaginal plug = day 1 of gestation). Maternal NOEL > 500 mg/kg/day (no effects observed). Developmental NOEL > 500 mg/kg/day (no effects observed). **No Adverse Effects Indicated. Unacceptable** (no MTD; no dose justification; no analysis of dosing material; data for pilot study not included). **Not Upgradeable**. (Silva, 5/19/88). Supplemental information in DPN 51317-026: record # 073121 contains data on homogeneity and stability of dosing material, and a pilot study at 0, 500, 1000 mg/kg/day, day 7-16 gestation, no evidence of any maternal toxicity; record # 073132 is a review of teratology studies, none of which used fenoxycarb as the test agent, and appears to be submitted as justification for not using MTD in teratogenicity studies. Registrant requested considering the following studies for justification of doses in rat teratogenicity study: five day oral dose range finding study (51317-020, 072974, which is exact duplicate of 51317-003, 064945) did not report rat strain, vehicle was tragacanth, only 10% mortality at 4000 mg/kg; rat subchronic study (51317-004, 064951) used a different strain of rats and vehicle was diet; rat metabolism study (51317-027, 073122 which is an exact duplicate of 51317-012, 064965) used a different strain of rat, vehicle was rape seed oil, 50 mg/kg/day for 28 days, no clinical signs, no necropsy reported. Study remains **Unacceptable** (for reasons stated above).

(DiBiasio and Gee, 7/14/89).

026 073121 "Pilot study for a teratogenicity study in rats (unpublished data)", (F. Hoffmann-La Roche & Co., Ltd., Department of Reproductive Toxicology, Basle, Switzerland, addendum to Lab Report No. B-104875, 5/12/83), Ro 13-5223/000 (Fenoxycarb), vehicle: Standard Solvent Vehicle (0.5% carboxymethylcellulose, 0.9% NaCl, 0.5% benzyl alcohol, 0.4% Tween 80 in distilled water), administered at 0, 500, and 1000 mg/kg by oral gavage, day 7 to 15 gestation, 10 rats/group, Maternal NOEL >1000 mg/kg, **no maternal adverse effects, fetal effects not reported**, not a guideline study, submitted as **supplemental** data for justification of dose selection for rat teratogenicity study (record # 064957), also includes data on homogeneity and stability of dosing solution but no analysis of dosing material. (DiBiasio and Gee, 7/13/89)

TERATOLOGY, RABBIT

009 029 064958 073124 "Embryotoxicity Study in Rabbits with Oral Administration of Ro 13-5223/000. Segment II Teratological Study", (F. Hoffmann-La Roche & Co. Ltd., Basle, Switzerland, Report # B-104 700, 2/13/84), Experiment A: Fenoxycarb technical (HKW 1668 Batch No. 18, 98% purity), was administered by gavage to mated Swiss hare rabbits (20/dose), at 0 (4% carboxymethylcellulose, 0.9% NaCl, 0.5% benzyl alcohol, 0.4% Tween 80 in distilled water), 30, 100, and 300 mg/kg/day from day 7 to 19 (inclusive) of gestation (day of copulation = day 1 of gestation). Experiment B: animals were treated at 0 and 200 mg/kg/day from day 7 to 19 of gestation (35/dose). Nominal Maternal NOEL > 300 mg/kg/day (no effects observed). Developmental NOEL > 300 mg/kg/day (no effects observed). **No adverse effect indicated**. Originally reviewed as **Not acceptable** (no MTD; no analysis of dosing material; no justification for dose selection; should have included historical control data regarding fetal malformations) and **Not upgradeable**. (Silva, 5/19/88). Record # 073124 contains a duplicate of 064958 plus stability and homogeneity data, the pilot study, and historical control data for tail abnormalities and cysts in rabbit brains. **Study remains Unacceptable** (no MTD, no analysis of dosing solutions). (DiBiasio and Gee, 7/13/89)

026 073132 "Maternal Toxicity: A Possible Etiological Factor in Embryo-Fetal Deaths and Fetal Malformations of Rodent-Rabbit Species", (Khera, (1985) Teratology **31**, 129-153). (See worksheet for discussion of article.) This study was submitted in support of a rabbit teratogenicity study DPN 51317-009, record # 064957 which was originally reviewed as unacceptable and not upgradeable (no MTD; no dose justification; no analysis of dosing material; data for pilot study not included) (M. Silva, 5/19/88). This journal article contains no studies which used Fenoxycarb as the test agent. This report appears to be submitted as justification for not using an MTD in their teratogenicity studies. CFR 40 guidelines state, however, that the highest dose must cause some evidence of maternal toxicity. (DiBiasio and Gee, 7/17/89)

029 073133 "Fixation-Induced Cyst-like Spaces in the Brains of Rabbit Foetus", (Niggeshulze, et al., (1977) Arch. Toxicol. **37**, 227-232). (See worksheet for discussion of article.) This study was submitted in support of DPN 51317-009, record # 064958 which was originally reviewed as **Not acceptable** (no MTD; no analysis of dosing material; no justification for dose selection; should have included historical control data regarding fetal malformations) and **Not upgradeable**. (M. Silva, 5/19/88). This supplemental information suggests the cyst-like findings in the original rabbit teratogenicity study (51317-009, 064958), which were not present in a dose-response manner, are artifacts of fixation. (DiBiasio and Gee, 7/17/89)

029 074847 "Cysts in Rabbit Foetal Brains. Malformations or Artifacts?", (Joosten, et al., (1981) Arch. Toxicol. **47**, 25-37). (See worksheet for discussion of article.) This study was submitted in support of DPN 51317-009, record # 064958 which was originally reviewed as **Not acceptable** (no MTD; no analysis of dosing material; no justification for dose selection; should have included historical control data regarding fetal malformations) and **Not upgradeable**. (M. Silva, 5/19/88). This supplemental information suggests that the cystic dilatation findings in the original rabbit teratogenicity study (51317-009, 064958), which were not present in a dose-response manner, are artifacts of fixation. (DiBiasio and Gee, 7/17/89)

GENE MUTATION

011 064960 "Mutagenicity Evaluation of the Insect Growth Regulator Ro 13-5223/000 in Salmonella typhimurium" (F. Hoffmann-La Roche & Co. Ltd., Basle, Switzerland; Report Number B-96 153; 3/9/81) Fenoxycarb (Lot No. 9, no purity stated) tested +/- S9 on Salmonella strains TA 1535, TA 1537, TA 1538, TA 98, and TA 100 in: 1) a Spot Test (0 or 240 ug/spot; 4 replicate plates), 2) a Plate Incorporation Test (0, 37.5, 75, 150, or 300 ug/plate; 4 replicate plates; repeat assay), and 3) a Plate Incorporation Test with Preincubation (0, 37.5, 75, 150, or 300 ug/plate; 4 replicate plates); **No mutagenicity; not acceptable and cannot be upgraded**-insufficient positive controls, too few dose levels, no evidence of cytotoxicity, and insufficient information on the test material. Davis 4/15/88.

** 011 064963 "Mutagenicity Evaluation of the Insect Growth Regulator Ro 13-5223/000 in Chinese Hamster Cells In Vitro in the Absence and Presence of a Mouse Liver Homogenate Metabolic Activation System" (F. Hoffmann-La Roche & Co. Ltd., Basle, Switzerland; Report Number B-96 728; 6/11/82) Fenoxycarb (Lot No. 18, purity = 98%) tested for the induction of mutations at the HGPRT locus in V79 cells at 0, 1, 5, or 25 ug/ml for 16 hours without activation and at 0, 25, 50, or 100 ug/ml for 5 hours with activation; a repeat assay was done. **No mutagenicity. Acceptable.** Davis 4/20/88.

030 073125, "Mutagenicity Evaluation of Fenoxycarb (Ro 13-5223/000) in the Ames Assay" (F. Hoffmann-La Roche & Company, Ltd., Basle, Switzerland, Report No. B-153'219, 11/8/88) Ro 13-5223/000 (fenoxycarb), Lot 2 (94.8% purity) was tested with Salmonella typhimurium in a reverse mutation assay using strains TA1535, TA1537, TA1538, TA97, TA98, TA100, TA102 by plate incorporation (0/DMSO, 15.8, 50, 158, 500, and 1580 ug/plate) for 2 days and preincubation (0/DMSO, 10, 31.6, 100, 316, 1000 ug/plate) for 30 minutes w/ and w/o activation by phenobarbital and beta-naphthoflavone stimulated rat liver S9 fraction; 4 plates/dose level; positive control materials (2 plates/material) for each strain; **no adverse effects noted (increase in revertants in TA1538 w/o S9 in plate incorporation only, attributed to low control values); **Acceptable.** (Duncan, Klein, and Gee, 5/15/89)

CHROMOSOME EFFECTS

011, 030 064962, 073127 "Mutagenicity Evaluation of the Insect Growth Regulator Ro 13-5223/000 with the Micronucleus Test in the Mouse" (F. Hoffmann-La Roche & Co. Ltd., Basle, Switzerland; Report Number B-96 679; 7/20/82) Fenoxycarb (Lot No. 18, purity = 98%) tested with two oral doses of 0, 500, 2500, or 5000 mg/kg of body weight using 3 Fullinsdorf Albino SPF mice/sex/group. Positive control mice were intraperitoneally injected twice with procarbazine hydrochloride. Dosing was 30 and 6 hours prior to sacrifice, following the Schmid protocol. 2000 polychromatic erythrocytes were scored for each animal. A repeat experiment increased the low dose to 1250 mg/kg. **No adverse effects noted** (no mutagenicity). **Not acceptable** and not upgradable - this protocol has been shown to provide inadequate sampling of cells. (Davis 4/20/88) Reviewed again after submittal of explanatory remarks (51317-030, Record 073127). No status change. (Klein and Gee, 6/7/89)

011 064964 "Chromosome Analysis of Human Peripheral Blood Lymphocytes After In Vitro Exposition of the Insect Growth Regulator Ro 13-5223/000" (F. Hoffmann-La Roche & Co. Ltd., Basle, Switzerland; Report Number B-96 681; 8/11/82) Fenoxycarb (Lot No. 18, purity = 98%) tested at 0, 0.4, 2.0, or 4.0 ug/ml in the absence of activation, and at 0, 1.0, 5.0, or 10.0 ug/ml in the presence of activation, using a primary culture of human lymphocytes; duplicate cultures; at least 200 cells scored for each dose level. **No mutagenicity; not acceptable and cannot be upgraded**-only three dose levels, only one exposure time and one sampling time, no evidence of cytotoxicity at high dose levels. Davis 4/20/88.

038 075432 "Chromosome analysis in human peripheral blood lymphocytes treated in vitro with the insect growth regulator Ro 13-5223/000 in absence and in presence of a metabolic activation system" (F. Hoffman-La Roche & Co. Ltd., Basle, Switzerland, Research Report # B-153'586, 2/21/89) Ro 13-5223/000

[fenoxycarb], Lot # 2, purity not stated, was tested with human peripheral blood lymphocytes that had been cultured for 24 hours, with and without activation by Aroclor-stimulated rat liver S9 fraction, 2 cultures/dose, 1 trial, 0 (DMSO), 25, 50, 100, or 150 ug/ml for 2 hours, with subsequent 24-hour incubation; **no adverse effects noted** (no structural aberrations); **unacceptable** (only one exposure time and one sampling time); **may be upgradeable** (with submission of evidence that metaphases resulting from the first mitosis after treatment were analyzed). Klein and Gee, 8/28/89.

DNA DAMAGE

** 011, 030 064961, 073126 "Mutagenicity Evaluation of the Insect Growth Regulator Ro 13-5223/000 (Ethyl [2-p(p-phenoxyphenoxy)ethyl] carbamate) with *Saccharomyces cerevisiae* strain D7 in a 'treat and plate' test" (F. Hoffmann-La Roche & Co. Ltd., Basle, Switzerland; Report Number B-95 594; 6/7/82) Fenoxycarb (Lot No. 16, purity = 95%) incubated for 3 hours +/- phenobarbital-stimulated rat liver S9 with yeast strain D7 for mitotic crossing over, mitotic gene conversion, and gene reversion (5 replicates for each) with 0 (DMSO), 0.017, 0.040, 0.17, or 0.40 mg of test material per ml of incubation mix; repeat assay done; **no adverse effects noted** (no mutagenicity, no gene conversion, no mitotic crossing over). Originally reviewed as not acceptable but upgradable (too few replicates; no information on the number of cells plated; numerous contaminated cultures; very low survival in one positive control group; missing positive control data). (Davis 4/19/88) Reviewed again with additional data (original and supplemental data, comments, and explanations) submitted (Volume 51317-030, Record 073126). **Status change to acceptable.** (Klein and Gee, 6/6/89)

NEUROTOXICITY

Not required at this time.

OTHER INFORMATION SUBMITTED

003 064950 "Influence of Ro 13-5223 on Acetylcholinesterase Activity in *Musca domestica*, Strain 13 (susceptible) in vitro," (F. Hoffman-La Roche Co., Ltd., no report number, memo dated 6/27/80). Acetylcholinesterase from heads of adult female flies (*M. domestica*, susceptible strain 13) was treated with Ro 13-5223 at $2.5 \times 10^{-5}M$ and $2.5 \times 10^{-4}M$ using acetylthiocholine iodide (21.7 mg/ml) as a substrate. Primicarb at the same molar concentrations served as a positive control while untreated enzyme was the negative control. Enzyme inhibition was measured after 2 hours incubation at 27C. **No adverse effect indicated.** NOEL > $2.5 \times 10^{-4}M$ (no effect at any level). There was no inhibition of acetylcholine hydrolysis in house flies in vitro by Ro 13-5223. **This study is supplementary.** M. Silva, 5/19/88.

015 066313 "Effect of Ro 13-5223/000 (IGR) on Plasma Cholinesterase in Rats," (F. Hoffman-La Roche, Ltd, Lab Report No. B-46202, 10/8/82). Fenoxycarb technical (Ro 13-5223/000, lot# 16, 95% pure) was administered by gavage to female Fullinsdorf rats (10/group) at 0 (vehicle = sodium-carboxymethylcellulose, tween 80, benzylalcohol, NaCl) and 5000 mg/kg. Positive controls were: 500 mg/kg carbaryl technical and 80 mg/kg chlorpyrifos technical. NOEL > 5000 mg/kg (No plasma cholinesterase inhibition was observed after 24 hours compared to the negative control. Positive controls were functional). **No adverse effect. This study is supplementary.** M. Silva, 5/9/88.

SUBCHRONIC, RAT

071; 144521; "28-Day Cumulative Oral Toxicity (Gavage) Study with CGA 114 597 in the Rat" (Suter, P., Research & Consulting Company AG, Itingen, Switzerland, Project No. 0S6283, Study No. 850908, 8/14/86).

CGA 114597 (Batch No. KA-4224/Chr 1-3, purity > 98%), mixed with 4% carboxymethylcellulose in distilled water, was administered daily by gavage to 10 SPF-bred Wistar rats per sex per dose level at concentrations of 0, 10, 50, 200, or 1000 mg/kg/day for 28 days. No animals died during the study. No treatment-related clinical signs were observed. Statistically significant decreases in mean red blood cell count and hemoglobin values in both males and females at 1000 mg/kg/day and in mean hematocrit values in females at 1000 mg/kg/day were observed. Statistically significant increases in mean alkaline phosphatase values in males at 1000 mg/kg/day and in females at 200 and 1000 mg/kg/day and in mean albumin to globulin ratios in males at 200 and 1000 mg/kg/day and in females at 50, 200, and 1000 mg/kg/day were observed. Statistically significant and dose-related increases in mean liver weight to mean brain weight ratios in males at 50, 200 and 1000 mg/kg/day and in females at 10, 50, 200 and 1000 mg/kg/day were observed. Histopathological examination revealed slight to moderate hypertrophy of the hepatocytes with the cytoplasm of these hepatocytes exhibiting slight to marked eosinophilia and slight to moderate follicular hyperplasia in the thyroid in both males and females at 1000 mg/kg/day. **No adverse effects.** NOEL (M)=10 mg/kg/day and NOEL (F)<10 mg/kg/day (based on increased mean liver weight to mean brain weight ratios). **Supplemental study** (test animals treated for only 28 days). (Corlett, 9/24/97)

070; 144519; "CGA-114597 Technical, 3-Month Oral Toxicity Study in Rats (Administration in Food)" (Bachmann, M., Ciba-Geigy Limited, Stein, Switzerland, Study No. 922116, 11/9/93). 821. CGA 114597 tech. (Batch No. 139044, purity=97.6%) was admixed to the feed at concentrations of 0, 30, 150, 750, or 3000 ppm and fed to 10 Sprague-Dawley derived rats per sex per dose (with an additional 10 animals per sex at 0 and 3000 ppm dose levels serving as a recovery group) continuously for 3 months (recovery group animals observed for an additional 4 weeks). No animals died during the study. No treatment-related clinical signs were observed. Statistically significant increases in mean cholesterol values at 750 and 3000 ppm and in mean alkaline phosphatase values at 3000 ppm in both males and females at week 14 were observed. Statistically significant increases in mean aspartate amino-transferase and mean alanine amino-transferase values at 3000 ppm in males at week 14 were also observed. Statistically significant increases in mean relative liver weights in males at 3000 ppm and in females at 750 and 3000 ppm were observed. Gross necropsy of animals sacrificed at week 14 revealed treatment-related enlarged livers in males at 3000 ppm and in females at 750 and 3000 ppm. Histopathological examination of animals sacrificed at week 14 revealed treatment-related minimal to moderate hypertrophy of hepatocytes and minimal to moderate hypertrophy of the follicular epithelium in the thyroid in males at 3000 ppm and in females at 750 and 3000 ppm. Within 4 weeks of recovery, histological changes in the liver and thyroid were fully reversible. **No adverse effects.** NOEL (M)=9.71 mg/kg/day (150 ppm) and NOEL (F)=10.14 mg/kg/day (150 ppm) (based on increased cholesterol values and histological changes in liver and thyroid). **Acceptable.** (Corlett, 9/29/97)